## REMARKS/ARGUMENTS

Claims 1-2, 5, 8, 10-12, 24, and 27 are active. Claims 6, 7, 9, and 13 and 19-23 have been withdrawn from consideration. Independent claims 1 and 27 have been amended for clarity and to recite specific steps involving control cells not resistant to oxaliplatin. Support is found at least in Example 1 of the specification. Claim 26 has been cancelled. No new matter has been added. The Applicants thank the Examiner for withdrawing the prior objections and objections. Favorable consideration of these amendments and allowance of this case are respectfully requested.

### Restriction/Election

The Applicants previously elected with traverse Group I as directed to a process of *in vitro* detection of resistant cancer cells to oxaliplatin treatment and to the following species: colorectal cancer, Bax and TNF. The Requirement has now been made FINAL. The Applicants respectfully request rejoinder and examination of any non-elected species upon an indication of allowability for a generic claim reading on the elected species. Rejoinder of claims in the non-elected groups which depend from or otherwise include all the limitation of an allowed elected claim is also respectfully requested, MPEP 821.04.

### Rejections—35 U.S.C. §102

Claim 26 was rejected under 35 U.S.C. §102(a) or (b) as being anticipated by Macpherson, et al., PAACR Annual Meeting 43:407; Arango, et al., PAACR Ann. Mtg. 43:457; or Fink, et al., PAACR Ann. Mtg. 43:457. These rejections are moot in view of the cancellation of this claim.

Rejection—35 U.S.C. §102

Claims 1, 2, 5, 10, 12, 24, and 27 were rejected under 35 U.S.C. §102(b) as being anticipated by Maurer, et al., Dig. Dis. Sci. 43:2641. This rejection is moot in view of the amendment of claims 1 and 27 which require steps absent from Mauer, et al., including:

a step of detecting the gene expression of the pro-apoptotic Bax and/or Bak proteins(s) in a cancer cell **and in a control cell not resistant to oxaliplatin**; and

a step of comparing the expression between the cancer cell and the control cell.

Accordingly, this rejection may now be withdrawn.

Rejections—35 U.S.C. §103

Claims 1 and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Maurer, et al., Dig. Dis. Sci. 43:2641, in view of Aggarwal, et al., J. Immunol. 160:1627. As indicated in the response to the anticipation rejections above, Mauer, et al. does not disclose all the method steps of the present invention, specifically the comparisons between gene expression of pro-apoptotic Bax and/or Bak proteins in cancer cells and in control cells not resistant to oxaliplatin. Aggarwal also does not disclose these steps since it was relied upon as disclosing quantitative PCR methods and is unconcerned with oxaliplatin resistance. Therefore, the prior art does not disclose or suggest all the elements of the invention, and this rejection must be withdrawn.

Furthermore, the prior art cannot suggest the invention because it is unconcerned with the problem solved by the invention. Namely, the present invention identifies a new marker whose level of expression in a cancer cell is correlated to the resistance or non-resistance to oxaliplatin. This is not disclosed or suggested by Maurer or by Aggarwal and these references cannot provide a reasonable expectation of success for the claimed methods.

On the other hand, the inventors have demonstrated that a lower level of expression of the pro-apoptotic Bax and/or Bak protein(s) in a cancer cell **taken by itself** compared to a control cell not resistant to oxaliplatin is indicative of resistance to oxaliplatin. Page 33, line 27 to page 34, line 2, of the specification, it is indicated that:

> Exposure to oxaliplatin induces an over-expression of Bax. This over-expression remaining comparable over all these lines, the inventors have tried to find out if the degree of Bax activation could account for the response of cells to oxaliplatin or if Bax definitely, **taken by itself**, couldn't be systematically associated with oxaliplatin sensitivity.

Page 34, line 21 of the specification disclose that:

> The inventors have demonstrated by means of figures 4A to 4C that the state of resistance or sensitivity of cells to oxaliplatin correlates well with the degree of activation of Bax.

Accordingly, this rejection may now be withdrawn, since the prior art does not disclose, suggest or provide a reasonable expectation of success for the claimed methods.

Rejections—35 U.S.C. §103

Claims 1, 2, 5, 8, 10, 12, 24 and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Maurer, et al., Dig. Dis. Sci. 43:2641, in view of Macpherson, et al., PAACR Ann. Mtg. 43:407 and Chao, et al., J. Exp. Med. 182:821.

Maurer has been addressed above and does not disclose all the method steps of the present invention, specifically the comparisons between gene expression of pro-apoptotic Bax and/or Bak proteins in cancer cells and in control cells not resistant to oxaliplatin.

The secondary references Macpherson and Chao are unconcerned about detecting the differences between Bax and Bgl expression between tumor and control cells and fail to disclose these elements of the invention as well.

Macpherson discloses that the down regulation of Bcl-xl (knock-out mediated by prior antisense) enhances the apoptotic response to oxaliplatin and consequently enhances

oxaliplatin cytotoxicity. However, this document does not suggest comparing the level of expression of the gene encoding Bcl-xl in tumor and control cells to determine the degree of oxaliplatin resistance.

Chao is also unconcerned with comparing Bax and Bcl expression between cancer and control cells since this document focuses on the parameter of **heterodimerization** of Bcl-2 or of Bax as evident from the citations below:

> This includes Bax, which heterodimerizes with Bcl-2 and **counters** its activity. The **ratio of Bcl-2/Bax** can determine whether a given cell will execute or ignore an apoptotic stimulus (7). ( emphasis added, page 821, 1st column).
>
> Given the existence of one regulatory **pair**, Bcl-2 **and** Bax, that an important question arises as to the rationale for further family members. (emphasis added; page 821, 2nd column).
>
> . . .in thymocytes from normal control mice, only 30% of Bax is heterodimerized with Bd-xL (Fig. 8A, upper panel), while the supernatant of that immunodepletion reveals that 70% of Bax is unbound (Fig. 8A, lower panel). In contrast, in the presence of the Bcl-xL transgene, a substantial portion of Bax (77%) is heterodimerized with Bcl-xL, while only 23% of Bax is unbound (Fig. 8B). The **heterodimerization of >50% of Bax with either Bcl-2 or Bcl-xL resulted in repression of cell death** in a cell line system (20). (emphasis added; page 825, 2nd column to page 821, 1st column).

Chao only suggests the importance the parameter heterodimerization of Bcl-2 or of Bax, and so the importance of **the ratio of the pair** Bcl-2/Bax compared to the unbound Bcl-2 or Bax to promote or to repress apoptosis in cell. In view of Chao, the person of ordinary skill would have used **the ratio of the pair** Bcl-2/Bax compared to the unbound Bax than the level of Bax expression **alone** as oxaliplatin resistance marker in cancer cell.

None of the cited documents suggests that in cancer cells, the level of Bax (or Bak) **taken alone** is indicative of oxaliplatin resistance; or as required by claim 1 "wherein reduced expression of said effector or marker gene in said cancer cell compared to said control cell indicates that said cancer cell is resistant to oxaliplatin".

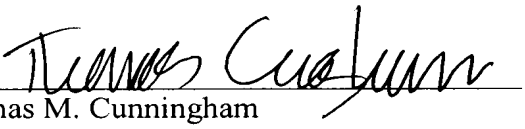
Therefore, the Applicants respectfully submit that this rejection cannot be maintained.

## Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Thomas M. Cunningham
Registration No. 45,394

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 03/06)